IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

PERNIX IRELAND PAIN DAC and PERNIX THERAPEUTICS, LLC,	)	
Plaintiffs,	)	REDACTED - PUBLIC VERSION
v.	)	C.A. No. 16-139-WCB
ALVOGEN MALTA OPERATIONS LTD.,	)	[redacted]
Defendant.	)	

BRIEF IN SUPPORT OF ALVOGEN'S MOTION FOR SUMMARY JUDGMENT OF INVALIDITY BY ANTICIPATION

Karen E. Keller (No. 4489)
Jeffrey T. Castellano (No. 4837)
David M. Fry (No. 5486)
Nathan R. Hoeschen (No. 6232)
SHAW KELLER LLP
I.M. Pei Building
1105 North Market Street, 12th Floor
Wilmington, DE 19801
(302) 298-0700
nhoeschen@shawkeller.com
Attorneys for Defendant

OF COUNSEL:
Matthew J. Becker
Chad A. Landmon
Thomas K. Hedemann
David K. Ludwig
AXINN, VELTROP & HARKRIDER LLP
90 State House Square
Hartford, CT 06103
(860) 275-8100
Seth I. Heller
Christopher M. Gallo
AXINN, VELTROP & HARKRIDER LLP
950 F. Street, N.W.
Washington, DC 20004
(202) 912-4700

Dated: March 16, 2018

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

Rules

Defendant Alvogen Malta Operations Ltd. ("Alvogen") respectfully requests that this Court enter summary judgment against Plaintiffs Pernix Ireland Pain DAC and Pernix Therapeutics, LLC (collectively, "Pernix") under Rule 56 of the Federal Rules of Civil Procedure. Claims 1-4, 11, 12, 17 and 19 of U.S. Patent No. 9,265,760 ("the '760 patent") and claim 1 of U.S. Patent No. 9,339,499 ("the '499 patent") (collectively, "the Asserted Claims") are invalid as a matter of law under pre-AIA 35 U.S.C. § 102 based upon each of U.S. Patent Appl. Pub. No. 2006/0240105 ("Devane") and U.S. Patent No. 8,808,740 ("Huang").

I. INTRODUCTION

The '760 and '499 patents (collectively, the "Patents-In-Suit") are directed to known methods of treating pain with a known formulation comprising the known active drug substance hydrocodone bitartrate. Recognizing just how much of the claimed subject matter was already known, the named inventors simply limited the claims by adding properties of the drug product when administered to patients also afflicted with liver impairment, known as hepatic impairment ("HI"). The Asserted Claims thus differ from the express disclosures in prior art only insofar as they recite inherent features of the prior art.

Given the foregoing, anticipation rests on a single issue – whether prior art teaching the treatment of the general population of pain patients with a known dosage form necessarily includes treating a sub-population of pain patients with HI. There should be no dispute on this point because Pernix's expert testified under oath that patients with pain inevitably include patients with HI as of the filing date

More specifically, the Asserted Claims recite methods for treating pain in a patient with mild or moderate HI comprising administering an extended-release ("ER") dosage form containing hydrocodone bitartrate as the only active ingredient. The claims also include "wherein" clauses that recite properties of the ER dosage form when administered to patients

with HI. In particular, the wherein clauses require that the "starting dose is not adjusted relative to a patient without [HI]," and/or that the dosage form "provides release profiles of hydrocodone that" meet certain post-administration pharmacokinetics ("PK") parameters in patents with HI as compared to patients without HI.

The Patents-In-Suit are based on a PK study in HI patients that administered a preferred embodiment dosage form called "HC-ER". There is no dispute that the named inventors did not invent the HC-ER formulation, but rather took it wholesale (including all of its ingredients and their concentrations) from a prior art patent to Devane. Likewise, the named inventors did not invent a method for treating pain with that dosage form – Devane already taught administering to treat pain. The Huang prior art patent also teaches an ER hydrocodone-only dosage form and associated methods for treating pain. Thus, there is no new use here. Instead, the Asserted Claims capture a known use in a sub-population of existing patients and simply add inherent properties in a failed effort to sidestep anticipatory prior art.

Accordingly, the Court should hold that each of Devane and Huang anticipates the Asserted Claims and enter summary judgment of invalidity under 35 U.S.C. § 102.

II. NATURE AND STAGE OF THE PROCEEDINGS

This is a patent action under the Hatch-Waxman Act. On March 4, 2016, Pernix sued Alvogen for infringement of the '760 patent in response to Alvogen's submission of ANDA No. 206986. (D.I. 1, ¶¶ 33-68.) On March 31, 2016, Pernix filed an Amended Complaint, adding the '499 patent to the action. (D.I. 22, ¶¶ 73-83.) On August 3, 2017, the Court issued a Markman order. (D.I. 69.) Fact and expert discovery are now closed, and the Court authorized the filing of this Motion on February 21, 2017. (D.I. 110.)

III. SUMMARY OF THE ARGUMENT

Pernix does not or cannot dispute the following critical facts.

- Each of Devane and Huang teaches methods of treating pain with an ER oral dosage unit having hydrocodone bitartrate as the only active ingredient. (Ex. 3, Devane at ¶ 70, Tables 6 and 7, claim 81; Ex. 4, Huang at [redacted] 2:21-49, 5:13-17, 7:25-28, claim 95.)[1]

- Devane's dosage unit is *identical* to the dosage unit referred to in the Patents-In-Suit as "HC-ER," which is the dosage unit referenced in Example 8 of the Patents-In-Suit and used in the HI study discussed therein. It is also identical to the commercial embodiment of the Patents-In-Suit – Zohydro® ER. (Ex. 7, Plaintiff's Resp. to RFA Nos. 10, 16-18.)

- As of 2012, the population of patients treated for pain with an ER opioid necessarily included patients with mild or moderate HI.[2] (Ex. 12, Gudin Dep. Tr. at 27:23-29:9.)

- Huang discloses an ER oral dosage unit having hydrocodone bitartrate as the only active ingredient. This dosage unit is [redacted] and has been used in an HI study. (Ex. 8, [redacted] at ¶¶ 5-8, Exs. A-C; Ex. 9, [redacted] at ¶ 7.)[3]

- Administering the ER hydrocodone dosage units of Devane and Huang to patients with mild or moderate HI necessarily satisfies the limitations recited in the wherein clauses of the Asserted Claims, i.e., not adjusting the starting dose and the PK parameters. (Ex. 10, Zohydro® ER Label at ALVHYDRO-PTX00013629; Ex. 5, [redacted] at ACT-HYD2-023236; Ex. 8, [redacted] Ex. B at PRNX00000068, PRNX00000071.)

The disclosures of patient populations treated for pain in Devane and Huang inherently include the sub-population of pain patients with HI. Federal Circuit law establishes that prior art disclosures that are broader than an inherent claim limitation satisfy the standard for inherency *provided* such disclosures include at least one embodiment that naturally and necessarily results

---

[1] Exhibit numbers refer to the Exhibits attached to the Declaration of Christopher M. Gallo in Support of this Motion for Summary Judgment.

[2] The reason this fact is undisputed is that Pernix needed to make a similar assertion to support is infringement allegations. According to Pernix's expert, "it is common for patients to whom the Alvogen Proposed ANDA Product is administered [i.e., pain patients] to be patients who suffer from mild or moderate hepatic impairment." (Ex. 19; Gudin Opening Report at ¶ 77.)

[3] [redacted] refer to the Declarations of [redacted] of [redacted] Per Rule 56(c)(1)(A), these declarations provide supporting evidence for Alvogen's motion. The documents appended to [redacted] declaration are admissible under Rules 901 and 803(6) of the Federal Rules of Evidence, as testified to by [redacted] (Ex. 8, [redacted]. at ¶¶ 1-5.)

in satisfaction of the limitation. See SmithKline Beecham v. Apotex Corp., 403 F.3d 1331, 1343 (Fed. Cir. 2005); Atlas Powder Co. v. Ireco, Inc., 190 F.3d 1342, 1347-49 (Fed. Cir. 1999). Such is the case here because it is undisputed that the population of pain patients as of 2012 necessarily includes patients with mild or moderate HI.

IV. FACTUAL BACKGROUND

A. Technological Setting of the Patents In-Suit

Hydrocodone bitartrate first appeared as an approved active pharmaceutical ingredient in the United States in 1943. (Ex. 10, Zohydro® ER Label at ALVHYDRO-PTX00013608 ("Initial U.S. Approval: 1943").) In the 2000s, various entities filed patent applications covering hydrocodone ER dosage forms. For example, Devane, published October, 26, 2006, and Huang, filed December 11, 2011, teach various hydrocodone ER dosage forms containing hydrocodone as the only active ingredient. (Ex. 3, Devane at ¶¶ 99-101; Ex. 4, Huang at 18:42-47:23.) For purposes of this Motion, the key dosage forms are Devane Example 3 (Tables 6 and 7) (called "HC-ER" in the Patents-In-Suit) and Huang [redacted] (Ex. 3, Devane at ¶¶ 99-101; Ex. 4, Huang at [redacted].)

The use of such dosage forms to treat pain was also well-known. Devane teaches that "[i]n embodiments which include drug compounds used for pain management, such as for example hydrocodone, the compositions and dosage forms of the present invention may provide continuous analgesia for up to 24 hours. . . ." (Ex. 3, Devane at ¶ 70.) Huang teaches a method of treating pain in human patients with a solid controlled-release dosage form comprising an opioid analgesic as an object of the alleged invention. (Ex. 4, Huang at 2:21-37, 5:13-17, 7:25-28.) Huang [redacted] is a controlled-release dosage form comprising hydrocodone bitartrate as the only active. (Ex. 4, Huang at [redacted].) [redacted] (Ex. 8, [redacted]. at ¶¶ 5-8; compare id. at

Ex. A with Ex. 4, Huang at [redacted]; Ex. 9, [redacted] at ¶ 7.)

A 2003 FDA Guidance document instructs drug companies to conduct HI studies to determine optimal dosing of drugs metabolized by the liver, which includes opioids such as hydrocodone. (Ex. 13, 2003 FDA Guidance at ACT-HYD2-023063.) As discussed further below, a company called Zogenix, Inc. conducted the FDA-required HI study on the HC-ER Example 3 formulation disclosed in Devane. [redacted] conducted such a study on [redacted]. (Ex. 8, [redacted]. at ¶ 7, Ex. B; Ex. 5, [redacted] at ACT-HYD2-023236.)

B. Patents-In-Suit

The Patents-In-Suit claim priority to July 31, 2012. Devane is prior art to these claims under 35 U.S.C. § 102(b). Huang is prior art under 35 U.S.C. § 102(e).

1. Development of Subject Matter Recited By the Asserted Claims

The '760 and '499 patents evergreen the embodiment of Devane's hydrocodone dosage forms referred to in the '760 and '499 patent specifications as HC-ER. Zogenix, Inc. initially obtained the rights to that dosage form in 2007 and sought to commercialize it as Zohydro® ER. (Ex. 11, Zogenix 30(b)(6) Dep. Tr. at 22:11-23, 24:16-18.) Zohydro® ER is identical to HC-ER in all respects. (Ex. 7, Plaintiff's Resp. to RFA Nos. 10, 16-18.)

As part of the FDA approval process for Zohydro® ER, Zogenix followed the 2003 FDA Guidance to conduct an HI study. (Ex. 15, PERNIX_HEP0015644.) Such HI studies were, of course, routine in the field. (Ex. 11, Zogenix 30(b)(6) Dep. Tr. at 46:13-48:21.) Based on the results of its HI study, Zogenix recognized that Zohydro® ER (aka HC-ER) exhibited certain inherent properties in patients with mild or moderate HI. Specifically, Zogenix observed that the pharmacokinetics (i.e., AUC and C_{max})[4] of this dosage form were only modestly increased in

[4] AUC is an abbreviation for area under the curve and connotes the total drug exposure in the

patients with mild or moderate HI relative to patients without HI. (Ex. 15, PERNIX_HEP0015629.) In other words, the liver sufficiently metabolized hydrocodone in patients with mild or moderate HI, thereby minimizing the risk of overdose. (Ex. 13, 2003 FDA Guidance at ACT-HYD2-023067-068.) This, in turn, meant that physicians need not reduce the starting dose of Zohydro® ER in mild and moderate HI patients. (Ex. 15, PERNIX_HEP0015629.)

2. Asserted Patents and Claims

Based on the foregoing, on July 31, 2015, Zogenix filed a patent application that disclosed the HC-ER dosage form from Devane and broadly claimed it in a method for treating pain in patients with mild or moderate HI. (Compare Ex. 1, '760 patent at 20:60-22:29 with Ex. 3, Devane at ¶¶ 99-101.) In fact, Zogenix copied the tables providing the formulation for HC-ER from Devane (Tables 6 and 7) into this application verbatim. (Id.) Because this dosage form and its use to treat pain were known, Zogenix's original claims included a "wherein" clause requiring non-adjustment of the starting dose in patients with mild or moderate HI. (See, e.g., Ex. 14, U.S. Appl. No. 14/815,219, Preliminary Amendment, filed July 31, 2015 at claim 26.)

On [redacted], during the pendency of this patent application, Pernix acquired the rights to the application as well as to Zohydro® ER. (Ex. 16, Zohydro® ER Purchase Agreement.) The patent application was important to Pernix because the composition patents listed in the Orange Book for Zohydro® ER were set to expire on November 1, 2019. (Ex. 17, Zohydro® ER Orange Book Entry.) In contrast, the patent application Pernix acquired, as well as its child, do not expire until July 25, 2033. (Id.) On December 24, 2015, the Patent Office allowed the '760 patent. Around the same time, Pernix filed the application leading to the '499

---

body over time. (Ex. 1, '760 patent at 11:12-14.) C_{max} is an abbreviation for concentration maximum and connotes the maximum concentration of drug in the body. (Id. at 11:63-65.)

patent. (Ex. 2, '499 patent at face page.)

In this lawsuit, Pernix's asserts claims 1-4, 11, 12, 17 and 19 of the '760 patent and claim 1 of the '499 patent. Claim 1 of the '760 patent recites:

> 1. A method of treating pain in a patient having mild or moderate hepatic impairment, the method comprising:
>
> administering to the patient having mild or moderate hepatic impairment a starting dose of an oral dosage unit having hydrocodone bitartrate as the only active ingredient, wherein the dosage unit comprises an extended release formulation of hydrocodone bitartrate, and **wherein the starting dose is not adjusted relative to a patient without hepatic impairment.**

(Ex. 1, '760 patent at claim 1.) On August 3, 2017, the Court construed the highlighted limitation as "[t]he dose prescribed to a patient with mild or moderate hepatic impairment when initiating treatment is not reduced due to that hepatic impairment relative to the dose prescribed to a patient without hepatic impairment when initiating treatment." (D.I. 69 at 2.)

All remaining Asserted Claims in the '760 patent, i.e., claims 2-4, 11, 12, 17 and 19, recite wherein clauses requiring certain "release profiles of hydrocodone," with AUC and C_{max} values that are comparable in patients with and without mild or moderate HI. Claims 2 and 11 are representative:

> 2. The method of claim 1, **wherein the dosage unit provides a release profile of hydrocodone that** does not increase average hydrocodone $AUC_{0\text{-}inf}$ in subjects suffering from mild hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 30%, and the release profile of hydrocodone does not increase average hydrocodone $AUC_{0\text{-}inf}$ in subjects suffering from moderate hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 50%.
>
> 11. The method of claim 9, **wherein the dosage unit provides a release profile of hydrocodone such that the average hydrocodone $AUC_{0\text{-}inf}$ per 20 mg of hydrocodone bitartrate dosed to subjects suffering from moderate hepatic impairment is in the range of about 352 ng*h/mL to about 666 ng*h/mL.**

(Id. at claims 2 and 11.) The remaining Asserted Claims of the '760 patent recite that the claimed dosage unit provides certain AUC or C_{max} values in patients with no, mild or

moderate HI, either in relative terms as in claim 2 or within specific ranges as in claim 11.

The lone Asserted Claim of the '499 patent, i.e., independent claim 1, recites:

> 1. A method of treating pain in a patient having mild or moderate hepatic impairment, the method comprising:
> administering to the patient having mild or moderate hepatic impairment an oral dosage unit having hydrocodone bitartrate as the only active ingredient, wherein the dosage unit comprises an extended release formulation of hydrocodone bitartrate,
> **wherein the dosage unit provides a release profile of hydrocodone that:**
> **does not increase average hydrocodone $AUC_{0\text{-}inf}$ in subjects suffering from mild hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 14%; and**
> **does not increase average hydrocodone $AUC_{0\text{-}inf}$ in subjects suffering from moderate hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 30%.**

(Ex. 2, '499 patent at claim 1.) Claim charts detailing prior art teachings for these and the other Asserted Claims on a limitation-by-limitation basis can be found in Exhibit 6.

V. ARGUMENT

There are no material facts in dispute with respect to anticipation by each of Devane and Huang. And as a matter of Federal Circuit law, the disclosures in Devane and Huang of administration of the disclosed hydrocodone dosage forms to all patients for the treatment of pain inherently disclose administration to the sub-population of patients treated for pain who also have mild or moderate HI. That was the conclusion reached on particularly analogous facts in Aventis Pharms., Inc. v. Barr Labs., Inc., 411 F. Supp. 2d 490, 519-24 (D.N.J. 2006), aff'd 208 Fed. Appx. 842-43 (Fed. Cir. 2006). And the result should be no different here.

A. Legal Principles

1. Summary Judgment

Under Rule 56(a) of the Federal Rules of Civil Procedure, "[t]he court shall grant summary judgment if the movant shows that there is no genuine dispute as to any material fact

and the movant is entitled to judgment as a matter of law." The moving party bears the burden of demonstrating the absence of a genuine issue of material fact. See Matsushita Elec. Indus. Co., Ltd. v. Zenith Radio Corp., 475 U.S. 574, 585-86 (1986). If the moving party has carried its burden, the non-movant must then "come forward with specific facts showing that there is a genuine issue for trial." Id. at 587 (internal quotation marks omitted). Although a court must draw all reasonable inferences in favor of the nonmoving party, a factual dispute is genuine only where "the evidence is such that a reasonable jury could return a verdict for the non-moving party." Id.; Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 278 (1986).

2. Anticipation

"A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention." Schering Corp. v. Geneva Pharms., 339 F.3d 1373, 1377 (Fed. Cir. 2003). "For prior art to anticipate a claim 'it must be sufficient to enable one with ordinary skill in the art to practice the invention.'" SmithKline, 403 F.3d at 1342. However, "[a]n anticipatory reference need only enable subject matter that falls within the scope of the claims at issue, nothing more." Schering, 399 F.3d at 1381.

"[A] prior art reference may anticipate when the claim limitation or limitations not expressly found in that reference are nonetheless inherent in it." Atlas Powder, 190 F.3d at 1347. That is, "if the prior art necessarily functions in accordance with, or includes, the claimed limitations it anticipates." Id. As such, "discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's function, does render the older composition patentably new to the discoverer." Id.; see also Titanium Metals Corp. of Am. v. Banner, 778 F.2d 775, 781-82 (Fed. Cir. 1985). Thus, summary judgment is appropriate where method claims are directed to "[n]ewly discovered results of known processes directed to the same purpose [as they] are not patentable because such results are inherent." Bristol-Myers

Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1376 (Fed. Cir. 2001) (affirming summary judgment of anticipation of claims directed to a method of treating cancer based on prior art disclosing the same method that did not recognize the treatment method was effective); In re Cruciferous Sprout Litig., 301 F.3d 1343, 1349-51, n.4 (Fed. Cir. 2002) (affirming summary judgment of anticipation of claims directed to a method of growing sprouts rich in glucosinolates because the patentee merely recognized a natural property of the claimed sprouts when harvested).

B. Each of Devane and Huang Anticipates the Asserted Claims

Devane and Huang teach each and every limitation recited by the Asserted Claims and enable their practice. Attached as Exhibit 6 are claim charts comparing the Asserted Claims to each of Devane and Huang. In addition, an analysis of the Asserted Claims follows.

1. Devane Meets Each and Every Limitation of the Asserted Claims

a. Independent Claims 1 and 12 of the '760 Patent

Devane expressly or inherently teaches each and every limitation of independent claims 1 and 12.

i. *Claims 1 and 12 - "a method of treating pain in a patient . . . ."*

The preamble of independent claims 1 and 12 of the '760 patent recites "a method of treating pain in a patient having mild or moderate hepatic impairment. . . ." To the extent the preamble limits these claims, Devane expressly teaches methods of treating pain in all patients requiring pain management. According to Devane, "[i]n embodiments which include drug compounds used for pain management, such as for example hydrocodone, the compositions and dosage forms of the present invention may provide continuous analgesia for up to 24 hours. . . ." (Ex. 3, Devane at ¶ 70.) Devane further discloses a clinical trial "evaluate[d] the safety, efficacy,

and PK of hydrocodone formulations in subjects immediately following bunionectomy study." (Id. at ¶ 104). Devane also claims "[a] method for the treatment of pain" comprising administering the claimed compositions. (Id. at claims 17 and 81.)

The remainder of the preamble recites that patients treated with the claimed method have "mild or moderate hepatic impairment." As discussed in detail below at Section V(B)(1)(a)(iii), Devane inherently teaches treating pain in such patients.

ii. *Claims 1 and 12 - " administering . . . [a starting dose of] an oral dosage unit having hydrocodone bitartrate as the only active ingredient, wherein the dosage unit comprises an extended release formulation of hydrocodone bitartrate"*

All Asserted Claims require the step of "administering to the patient having mild or moderate hepatic impairment a starting dose of an oral dosage unit having hydrocodone bitartrate as the only active ingredient, wherein the dosage unit comprises an extended release formulation of hydrocodone bitartrate." As with the preamble, Devane inherently teaches administering an ER hydrocodone-only oral dosage unit to patients *with mild or moderate HI*. (See infra Section V(B)(1)(a)(iii).)

As to the remaining aspects of this limitation, Devane expressly teach administering a starting dose of such a dosage unit to patients generally. Devane states, "[i]n embodiments which include drug compounds used for pain management, such as for example hydrocodone, the compositions and dosage forms of the present invention may provide continuous analgesia for up to 24 hours. . . ." (Ex. 3, Devane at ¶ 70.) Devane provides an example of "a dosage form of the present invention" at Example 3, which is an ER oral dosage unit having hydrocodone bitartrate as the only active ingredient. (Id. at ¶ 104.) It is undisputed that the dosage form in Example 3 of Devane is identical to the dosage form called HC-ER in Example 8 of the Patents-In-Suit, which Pernix has commercialized as Zohydro® ER. (Ex. 7, Plaintiff's Resp. to RFA

Nos. 10, 16-18.) Further, the first dose of this dosage form administered to patients treated for pain management is "a starting dose." Thus, Devane expressly teaches administering a starting dose of an ER hydrocodone-only oral dosage unit to a patient.

iii. *Claims 1 and 12 – "in patients with mild or moderate hepatic impairment"*

As discussed above, Devane expressly teaches administering dosage forms "of the present invention," including what the Patents-In-Suit call HC-ER, to patients with pain generally. (Ex. 3, Devane at ¶¶ 70, 104, claims 17 and 81.) Under Federal Circuit principles of inherency, this disclosure of administering HC-ER to *all* pain patients inherently discloses administering this dosage form to the sub-population of patients with mild or moderate HI. Indeed, the Federal Circuit affirmed a prior decision holding exactly this way in Aventis, 411 F. Supp. 2d at 519-24.

First and foremost, it is black letter law that "a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." SmithKline, 403 F.3d at 1343. In SmithKline, the Federal Circuit noted that a prior art disclosure necessarily leading to the claimed subject matter in some but not all embodiments satisfies the standard for inherency. Id.

In Aventis, the court applied this standard to find pharmaceutical method of treatment claims anticipated based on facts highly analogous to this case. The claim at issue there recited a method of treating allergic rhinitis in patients with HI by administering fexofenadine while avoiding cardiac events. Aventis, 411 F. Supp. 2d at 519. Similar to the prior art here, a prior art patent to Carr broadly disclosed that fexofenadine could be administered with suitable pharmaceutical carriers to treat allergic rhinitis in humans. Id. at 519-24. (See also Ex. 18, U.S. Patent No. 4,254,129 ("Carr") at 5:1-16, 6:1-3.) And like Devane and Huang here, Carr also

claimed a method of treatment – specifically, a method for treating all allergic rhinitis patients with fexofenadine. Id. at 519-24. (See also Ex. 18, Carr at claim 11.) And as in this case, the patentee in Aventis asserted that the broad treatment population included some percentage of patients afflicted with HI in order to prove infringement. Id. at 516.

Applying the Federal Circuit's principles of inherent anticipation, the Aventis court held that "treating hepatically impaired patients is necessarily present in the teaching of the Carr reference, which discloses a method for treating all patients; *it need not be present in every instance of use or practice* of the Carr method."[5] Id. at 522 (emphasis added). This conclusion follows from the Federal Circuit's clarification in SmithKline that an inherent disclosure need not be present in every instance of practicing the prior art. Rather, a defendant "merely [needs to show] that the disclosure [of the prior art] is sufficient to show that the natural result flowing from the operation as taught [in the prior art] would result in the claimed product." SmithKline, 403 F.3d at 1343. See also Atlas Powder, 190 F.3d at 1347-49 (finding anticipation when some prior art embodiments necessarily satisfied the claimed aeration property while others did not). Finally, the Aventis court also concluded that the alleged cardiac "discovery" of the patentee was merely a previously unappreciated property of the prior art treatment method directed to the *same* purpose, i.e., treating allergic rhinitis, and thus was not patentably new. Id. at 523 (citing Atlas Powder, 190 F.3d at 1347; Bristol-Myers, 246 F.3d at 1376).

The case of Perricone v. Medicis Pharm. Corp., 423 F.3d 1368 (Fed. Cir. 2005), provides still further guidance. In Perricone, the Federal Circuit upheld the district court's finding that a prior art patent to Pereira disclosing a cosmetic composition for topical application to the skin inherently anticipated claims to methods of preventing skin sunburn and skin aging by applying

[5] The decision in Aventis was at the preliminary injunction stage.

the same composition. Id. at 1379-80. The patentee argued that there was no inherent anticipation because Pereira did not "disclose any benefit directed to skin sunburn, or any of the other specific skin disorders." Id. at 1376. The court rejected this argument, explaining "[u]nder the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claims limitations, it anticipates." Id. at 1376-78 (quoting Cruciferous, 301 F.3d at 1349). "Thus, when considering a prior art method, the anticipation doctrine examines the natural and inherent results in that method without regard to the full recognition of those benefits or characteristics within the art field at the time of the prior art disclosure." Id. at 1378.

Although Perricone upheld the validity of certain claims directed to *treating* sunburn, these claims are distinguishable from the Asserted Claims here. Perricone upheld them because they were arguably directed to a new use of the prior art compound. Id. at 1378-79. Here, there is no such argument. Devane discloses the same exact use as that claimed: treating pain. Simply because the claimed methods also extend to treating a subpopulation of pain patients with mild or moderate HI does not render them "new uses." Further, discussion of the inherency standard with respect to the treating sunburn claims in partial dissent was consistent with Aventis, SmithKline and Atlas. Id. at 1381-86 (Bryson, J., partially concurring, partially dissenting).

The principles and reasoning of the above cases apply with equal force here. There is no dispute that Devane and Huang disclose administering an ER hydrocodone-only oral dosage unit to patients to treat pain generally. Just as in Aventis, there is also no dispute that the population of pain patients receiving such treatment inevitably includes patients with mild or moderate HI. (Ex. 12, Gudin Dep. Tr. at 27:23-29:9.) Therefore, and just as in Aventis, application of the Devane or Huang methods to the sub-population of patients with mild or moderate HI is the "natural result flowing from the operation as taught. . . ." SmithKline, 403 F.3d at 1343. Using

the terminology of Perricone, the prior art disclosure "encompasses" the claimed methods of treating pain in the sub-population of patients with mild or moderate HI. Put differently, and as articulated by the partial concurrence and dissent in Perricone, "[t]his is not a case in which the patentee is claiming a method that consists of a new way of using a previously known product in order to achieve a new result." Id. at 1383 (Bryson, J., partially concurring, partially dissenting). Rather, the patentee is claiming a method of using a known product in a known way, i.e., to treat pain. Inherency is thus present here as a matter of law.

In summary, applying the principles of inherent anticipation articulated by the Federal Circuit and the Aventis court to the undisputed facts of this case leads to the conclusion that Devane inherently discloses administering HC-ER to patients with mild or moderate HI. Inherency is therefore present as a matter of law.

iv. *Claim 1 – "wherein the starting dose is not adjusted relative to a patient without hepatic impairment"*

Administration of Devane's dosage form to patients with mild or moderate HI also necessarily satisfies the wherein clause requiring non-adjustment of the starting dose. The Court adopted Pernix's proposed construction of this phrase to mean that "[t]he dose prescribed to a patient with mild or moderate hepatic impairment when initiating treatment is not reduced ***due to that hepatic impairment*** relative to the dose prescribed to a patient without hepatic impairment when initiating treatment." (D.I. 69 at 2 (emphasis added).) The reason a starting dose is not adjusted "due to" mild or moderate HI with respect to the claimed ER hydrocodone oral dosage unit is that the claims cover any dosage unit that necessarily produces similar AUC and C_{max} values in patients with and without mild or moderate HI. In other words, there is no required dose adjustment based on the body's physiological and inherent response to dosage forms covered by the claims.

The Devane dosage form is one such example. When administered to the sub-population of pain patients with HI, Devane's Example 3 dosage form must necessarily meet the non-adjustment limitation because Devane's dosage form is identical to the HC-ER dosage form used in Example 8 of the '760 and '499 patents and to Zohydro® ER, both of which Pernix asserts are covered by the Asserted Claims. It is well-settled that "[p]roducts of identical chemical composition can not [sic] have mutually exclusive properties." In re Spada, 911 F.2d 705, 708-09 (Fed. Cir. 1990) (citing In re Papesch, 315 F.2d 381, 391 (CCPA 1963) (a chemical composition and its properties are inseparable)). If Pernix's Zohydro® ER and HC-ER satisfy this limitation, as Pernix asserts, (see Ex. 1, '760 patent at 23:27-38; Ex. 10, Zohydro® ER Label at ALVHYDRO-PTX00013629), then the identical Devane dosage form necessarily satisfies it as well. See Spada, 911 F.2d at 708-09.

v. *Claim 12 – "wherein the dosage unit provides a release profile. . . ."*

Independent claim 12 of the '760 patent recites "wherein the dosage form provides a release profile of hydrocodone" providing certain AUC and C_{max} values. For the same reasons Devane's dosage form satisfies the wherein clause of claims 1, it likewise satisfies these limitations. Once again, identical compositions must necessarily produce identical properties. Id. The claimed AUC and C_{max} parameters recited by the wherein clauses of independent claim 12 are nothing more than unappreciated properties inherent in the teachings in Devane.

b. Claims 2-4, 11, 17 and 19 of the '760 patent

Dependent claims 2-4, 11, 17 and 19 of the '760 patent recite "wherein the dosage form provides a release profile of hydrocodone" providing certain AUC and C_{max} values. For the same reasons Devane's dosage form satisfies the wherein clauses of claims 1 and 12, it likewise satisfies these limitations. Once again, identical compositions must necessarily produce identical

properties. Id. The claimed AUC and C_{max} parameters recited by the wherein clauses of dependent claims 2-4, 11, 17 and 19 are nothing more than unappreciated properties inherent in the teachings in Devane.

c. Claim 1 of the '499 patent

Finally, Devane indisputably anticipates independent claim 1 of the '499 patent. As reflected in the claim charts (Ex. 6), the limitations preceding the final wherein clause of this claim are virtually identical to independent claims 1 and 12 of the '760 patent. They are satisfied by Devane for the same reasons set forth above at Sections V(B)(1)(a)(i)-(iii). With respect to the wherein clause, reciting "wherein the dosage unit provides a release profile of hydrocodone that" provides certain AUC and C_{max} values, Devane necessarily satisfies that limitation for the reasons set forth at Sections V(B)(1)(a)(v) and V(B)(1)(b). Like the other wherein clauses in the '760 patent, this wherein clause simply recites an unappreciated property of administering the dosage form of Devane.

2. Huang Meets Each and Every Limitation of the Asserted Claims.

a. Independent Claims 1 and 12 of the '760 patent

Huang expressly or inherently teaches each and every limitation of independent claims 1 and 12.

i. *Claims 1 and 12 - "a method of treating pain in a patient . . ."*

The preamble of claim 1 of the '760 patent recites "a method of treating pain in a patient having mild or moderate hepatic impairment. . . ." As with Devane, and as discussed below at Section (V)(B)(1)(b)(iii), Huang inherently satisfies the limitation requiring treating pain in patients *with mild or moderate HI*.

With respect to treating pain generally, Huang states "[i]t is a[n] . . . object of certain

embodiments of the present invention to provide a method of treating pain in human patients with a solid controlled release dosage form comprising an opioid analgesic. . . ." (Ex. 4, Huang at 2:21-25; see also id. at 2:26-29, 2:34-37, 7:25-28.) Like Devane, Huang also claims a method of treating pain "comprising administering to the subject the solid controlled release dosage form according to claim 1." (Id. at claim 95.)

ii. *Claims 1 and 12 - " administering . . . [a starting dose of] an oral dosage unit having hydrocodone bitartrate as the only active ingredient, wherein the dosage unit comprises an extended release formulation of hydrocodone bitartrate"*

Huang also teaches "administering to the patient having mild or moderate hepatic impairment an oral dosage unit having hydrocodone bitartrate as the only active ingredient, wherein the dosage unit comprises an extended release formulation of hydrocodone bitartrate."

As previously mentioned, Huang teaches that "[i]t is a[n] . . . object of certain embodiments of the present invention to provide a method of treating pain in human patients with a solid controlled release dosage form comprising an opioid analgesic. . . ." (Ex. 4, Huang at 2:21-25; see also id. at 2:26-29, 2:34-37, 7:25-28.) Huang [redacted] is a solid controlled release dosage form comprising hydrocodone. It undisputedly qualifies as an ER oral dosage unit having hydrocodone bitartrate as the only active ingredient. (Id. at [redacted].) It is also undisputed that [redacted] is identical to the formulation [redacted] (Ex. 8, [redacted]. at ¶¶ 5-8, Exs. A-C; Ex. 9, [redacted] at ¶ 7.) [redacted] also falls within the scope of Huang's claimed method of treating pain, as it is encompassed by Huang's claim 1. (Ex. 4, Huang at [redacted].) Use of [redacted] in methods for treating pain includes administering a starting dose. Thus, Huang expressly teaches administering an ER hydrocodone-only oral dosage unit, including a starting dose of the same.

Huang also inherently teaches administering its [redacted] to patients with mild or

moderate HI. The following section addresses this point in detail.

iii. *Claims 1 and 12 – "in patients with mild or moderate hepatic impairment"*

Huang inherently teaches administering [redacted] to patients with mild or moderate HI to treat pain. As previously mentioned, Huang expressly teaches administering [redacted] to patients with pain generally. (Ex. 4, Huang at 2:21-49, 5:13-17, 7:25-28, claim 95.) For the same reasons discussed above for Devane at Section V(B)(1)(a)(iii), Huang's disclosure of administering [redacted] to the population of patients with pain necessarily includes administering [redacted] to a sub-population of patients with mild or moderate HI to treat pain.

iv. *Claim 1 – "wherein the starting dose is not adjusted relative to a patient without hepatic impairment"*

Huang [redacted] also inherently satisfies the wherein clause requiring non-adjustment of the starting dose. As discussed earlier, the Court construed this term to mean that the starting does is not reduced due to the patient's mild or moderate HI. Supra at Section V(B)(1)(a)(iv). The 2003 FDA Guidance makes clear that dosage adjustments are only necessary in HI patients when "the effect of hepatic impairment on the PK of the drug is obvious (e.g., two-fold or greater increase in AUC). . . ." (Ex. 13, 2003 FDA Guidance at ACT-HYD2-023067.) The guidance also states "[a] conclusion that there is ***no effect*** (really, no clinically important effect) of hepatic impairment on the drug's PK" may be supported by "the employment of a standard 90 percent confidence interval of 80-125 percent for AUC and C_{max}." (Id. at ACT-HYD2-023068 (emphasis in original).) Post-filing PK data derived from a clinical study on HI patients who received Huang's [redacted] demonstrates that mild and moderate HI has no clinically important effect on the PK of

[redacted].[6] (Ex. 5, [redacted] at ACT-HYD2-023236; Ex. 8, [redacted] Ex. B at PRNX00000068, PRNX00000071). Huang's [redacted] provides the following $AUC_{0\text{-}inf}$ and C_{max} values in patients with and without mild or moderate HI per 20 mg tablet:

PK Parameters	Patients without HI	Patients with mild HI	Patients with moderate HI
$AUC_{0\text{-}inf}$	[redacted]		
C_{max}			

Applying FDA's 80-125 standard to these values provides a range of no clinical effect for AUC of 273.6 to 427.5 ng*hr/mL and a range of no clinical effect for C_{max} of 12.8 to 20 ng/mL. Thus, not only does [redacted] come nowhere near the two-fold increase identified in the 2003 FDA Guidance as requiring dose adjustment, it easily falls within FDA's standard for no clinically important effect of HI. And that is precisely why [redacted] expressly states that dose adjustment is unnecessary in patients with mild or moderate HI. (Ex. 5, [redacted] at ACT-HYD2-023226.)

v. *Claim 12 – "wherein the dosage unit provides a release profile. . . ."*

Independent claim 12 of the '760 patent recites "wherein the dosage form provides a release profile of hydrocodone" providing certain AUC and C_{max} values. Huang's [redacted], when administered to patients with mild or moderate HI, also meets all of the AUC and C_{max} values recited by the wherein clauses of this claims. As the data referenced above demonstrates, [redacted] provides release profiles with AUC values falling within the ranges recited by claim 12 of the '760 patent. (See also Ex. 6.) Specifically, [redacted] achieves a decrease

[6] It is, of course, entirely proper to rely upon secondary references published after the Patents-In-Suit to prove inherent properties of a prior art composition. See, e.g., Monsanto Tech. LLC v. E.I. DuPont de Nemours & Co., 878 F.3d 1336, 1346 (Fed. Cir. 2018) (finding it proper for the PTAB to rely on unpublished, post-filing extrinsic evidence that "support[ed] what is 'necessarily present' in a prior art's teaching").

of 9.4% and an increase of 14% in mean $AUC_{0\text{-}inf}$ in patients with mild and moderate HI, respectively, compared to patients without HI, and a decrease of 4.4% and an increase of 6.3% in mean C_{max} in patients with mild and moderate HI, respectively – all meeting the claimed deltas in mean $AUC_{0\text{-}inf}$ and C_{max} recited by claim 12 of the '760 patent. (Id.)

In sum, the "wherein" clause recited by Asserted Claim 12 of the '760 patent merely capture unappreciated properties that are necessarily attributable to the Huang dosage form when administered to patients with mild or moderate HI in order to treat pain. They too are inherent.

b. Claims 2-4, 11, 17 and 19 of the '760 patent

Dependent claims 2-4, 11, 17 and 19 of the '760 patent recite "wherein the dosage form provides a release profile" providing certain relative or absolute AUC and C_{max} values. Based on the same $AUC_{0\text{-}inf}$ and C_{max} values for Huang's [redacted] discussed with respect to claim 12 above, [redacted] also meets all of the AUC and C_{max} values recited by the wherein clauses of these claims. (See Ex. 6.) Again, therefore, the "wherein" clauses recited by Asserted Claims 2-4, 11, 17 and 19 of the '760 patent merely capture unappreciated properties that are necessarily attributable to the Huang dosage form when administered to patients with mild or moderate HI in order to treat pain. Thus, they too are inherent.

c. Claim 1 of the '499 patent

For all of these same reasons, Huang also anticipates independent claim 1 of the '499 patent. The limitations preceding the final wherein clause of this claim are satisfied by Huang for the same reasons set forth above at Sections V(B)(2)(a)(i)-(iii). With respect to the "release profile" wherein clause, Huang necessarily satisfies that limitation for the reasons set forth at Sections V(B)(2)(a)(v) and V(B)(2)(b).

3. Devane and Huang Enable Practice of the Claimed Subject Matter

Finally, there can be no dispute that Devane and Huang enable practice of the Asserted

Claims. Both Devane and Huang provide detailed disclosures concerning how to make their ER hydrocodone dosage forms, including an express list of their ingredients and respective concentrations, as well as disclosures regarding using their dosage forms to treat pain. (Ex. 3, Devane at, e.g., ¶¶ 63-74, 99-106; Ex. 4, Huang at, e.g., 14:55-17:5, 18:40-47:23.) And once again, the Patents-In-Suit copied the Devane dosage form verbatim. Accordingly, Devane and Huang teach and enable each and every limitation of the Asserted Claims.

VI. CONCLUSION

For the reasons set forth above, the Court should enter summary judgment that claims 1-4, 11, 12, 17 and 19 of the '760 patent and claim 1 of the '499 patent are invalid under pre-AIA 35 U.S.C. § 102.

Respectfully submitted,

SHAW KELLER LLP

/s/ Nathan R. Hoeschen

Karen E. Keller (No. 4489)
Jeffrey T. Castellano (No. 4837)
David M. Fry (No. 5486)
Nathan R. Hoeschen (No. 6232)
I.M. Pei Building
1105 North Market Street, 12th Floor
Wilmington, DE 19801
(302) 298-0700
nhoeschen@shawkeller.com
Attorneys for Defendant

OF COUNSEL:
Matthew J. Becker
Chad A. Landmon
Thomas K. Hedemann
David K. Ludwig
AXINN, VELTROP & HARKRIDER LLP
90 State House Square
Hartford, CT 06103
(860) 275-8100

Seth I. Heller
Christopher M. Gallo
AXINN, VELTROP & HARKRIDER LLP
950 F. Street, N.W.
Washington, DC 20004
(202) 912-4700

Dated: March 16, 2018